Br J Vener Dis 1982;**58**:117-20

Rosaramicin and tetracycline in the treatment of non-gonococcal urethritis

A comparison of clinical and microbiological results

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SUMMARY The clinical and microbiological outcome of the treatment of 94 men for uncomplicated non-gonococcal urethritis (NGU) was studied. Rosaramicin 250 mg six hourly for seven days was given to 46 men and tetracycline 250 mg six hourly for seven days to 48 men; the follow-up period was up to six weeks. Complete resolution of the clinical signs of infection was seen in 40 (87%) of the men treated with rosaramicin and in 37 (77%) of those treated with tetracycline. *Chlamydia trachomatis* was eliminated from 17 of the 18 men treated with rosaramicin and from all of the 16 men treated with tetracycline. *Ureaplasma urealyticum* was eliminated from 12 of the 14 men treated with rosaramicin and from 15 of the 19 receiving tetracycline. Clinical recovery correlated well with the elimination of *C trachomatis* but less well with that of *U urealyticum*. The two antimicrobial agents were equally effective in the therapy of NGU, but gastrointestinal side effects were significantly more common in men treated with rosaramicin.

Introduction

Non-gonococcal urethritis (NGU) is one of the commonest sexually transmitted diseases. There is a substantial body of evidence from isolation studies, serology, and response to antimicrobial therapy to indicate that *Chlamydia trachomatis* causes 35-60% of cases.[1] The evidence implicating *Ureaplasma urealyticum* is less compelling, but this organism is believed to cause some cases.[2] At least one-quarter of NGU infections are of unknown aetiology.

Many years ago, empirical studies clearly showed that the tetracylines were clinically highly effective in the treatment of NGU.[3] These agents show in-vitro activity against *C trachomatis* and against many strains of *U urealyticum*, and studies of men with NGU treated with tetracyclines have linked clinical improvement with the eradication of one or both of these organisms.[4] Patients with NGU who harbour neither *C trachomatis* nor *U urealyticum* show the poorest clinical response to treatment.[5] The macrolide antibiotic, erythromycin, also gives good results in the treatment of NGU. Its in-vitro activity against *C trachomatis* is reflected by its efficacy in chlamydia-positive NGU, and it also gives good results in chlamydia-negative NGU.[6] It is active in vitro against many strains of *U urealyticum*, but its clinical efficacy against this organism has not been studied.

Rosaramicin is a macrolide antibiotic which is active against *Neisscria gonorrhoeae* and has given good clinical results in the treatment of gonorrhoea.[7] It is also active against both *C trachomatis* and *U urealyticum*. Good results have been obtained in the treatment of both chlamydia-positive and chlamydia-negative NGU[8]; its efficacy against *U urealyticum* associated with NGU has not yet been studied. In this investigation rosaramicin was compared with tetracycline in the treatment of NGU with regard to its clinical efficacy and action against *C trachomatis* and *U urealyticum*.

Patients and methods

CLINICAL PROCEDURES

A group of men with uncomplicated NGU was studied. The criteria for inclusion in the investigation were: (1) the presence of a visible urethral discharge; (2) a Gram stain of the discharge showing no intracellular diplococci and $\geqslant 5$ polymorphonuclear leucocytes (PMNL) per high-power field at $\times 1000$ magnification; (3) negative culture result of this material for *N*

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Accepted for publication 18 September 1981

gonorrhoeae; (4) no antibiotic treatment for four weeks before enrolment; and (5) no clinical evidence of serious systemic disease nor history of allergy to tetracyclines or macrolides. Informed consent to the investigation was obtained from each patient.

At first attendance, a history was taken and the patient fully examined. Specimens were collected as follows: (1) urethral material was collected with a plastic loop (Nunc Products Ltd) and spread on a glass slide for Gram staining; (2) a second specimen was used to inoculate a culture plate for *N gonorrhoeae*; (3) an endourethral wire-mounted cottonwool swab (Medical Wire and Equipment Co) was passed 1-2 cm into the urethra, removed, and cut off into a tube of mycoplasma transport medium; (4) a second wire-mounted swab was passed 4-5 cm into the urethra, removed, and cut off into a tube of chlamydia transport medium; (5) in a two-glass urine test suspended material in the first glass was examined microscopically for PMNL and the midstream specimen examined for albumin and sugar and cultured for urinary pathogens; and (6) blood was collected for serological tests for syphilis, routine haematology, and blood chemistry.

TREATMENT ALLOCATION

After a diagnosis of NGU had been made the patients were assigned by random numbers to two treatment schedules: rosaramicin 250 mg six hrly for seven days or tetracycline 250 mg six hrly for seven days. Follow-up examinations were performed on all patients on the completion of treatment (day 7) and two weeks after (day 21); when possible, a third follow-up examination was performed four weeks later (day 49). On each occasion after clinical examination specimens (1) to (5) were examined as described above. Serological tests for syphilis, if initially giving negative results, were not repeated during the study, and haematological and biochemical tests were repeated only on day 7. Neither the patient nor the physician knew which drug had been taken, and the data were evaluated blindly. The two treatment groups were similar for demographic data and previous history of STD.

LABORATORY PROCEDURES

N gonorrhoeae was cultured on a selective medium.[9] Cell culture for *C trachomatis* was performed by centrifugation of specimens on to McCoy cells pretreated with idoxuridine followed by incubation and examination for chlamydial inclusion bodies.[10] A semi-quantitative technique modified from the method of Taylor-Robinson *et al* [11] was used for the culture of *U urealyticum*; tubes of liquid culture showing pH change were subcultured to solid media to confirm the presence of *U urealyticum*.

EVALUATION CRITERIA

Evaluation of the clinical response to therapy was performed after the completion of follow up and was classified as follows:

Complete resolution—disappearance of symptoms, no visible urethral discharge, <5 PMNL per field on microscopy of a Gram-stained urethral smear, and urine free from suspended matter;

Improvement—symptoms still present but no discharge, or symptoms absent but discharge still present although decreasing;

Treatment failure—no improvement in symptoms or signs and reinfection unlikely (no further sexual contact admitted);

Indeterminate—no improvement in symptoms or signs but reinfection possible, responses not falling into the other categories.

Microbiological evaluation was based on the results of culture for *C trachomatis* and *U urealyticum* before and after treatment.

STATISTICAL METHODS

The Mann-Whitney U test (two-tailed) was used to compare treatment differences for final clinical and microbiological evaluation. The Fisher exact test (two-tailed) was used for the assessment of side effects of therapy.

Results

A group of 137 men with NGU met the criteria for inclusion in the study but eight did not return after the first visit and a further 35 either failed to complete their follow-up examinations for at least 21 days or had incomplete laboratory data. Thus 94 men were studied fully; 46 were treated with rosaramicin and 48 with tetracycline.

CLINICAL RESPONSE

Complete resolution of the clinical signs of infection occurred in 40 (87%) of the 46 men treated with rosaramicin and in 37 (77%) of the 48 men treated with tetracycline (table I). These differences are not significant.

MICROBIOLOGICAL RESPONSE

Chlamydia trachomatis

C trachomatis was isolated from 18 of 46 (39%) men before treatment with rosaramicin (in 16 as the sole pathogen and in two in association with *U urealyticum*). Chlamydia were reisolated from one of these 18 patients during the follow-up period; he showed evidence of persistent urethritis and denied sexual intercourse since therapy. *C trachomatis* was isolated from 16 of 48 (33%) men before treatment

TABLE I *Clinical response of men with NGU treated with rosaramicin or tetracycline*

Treatment schedule	*No of patients*				
	Complete resolution of infection	*Incomplete resolution*	*Treatment failure*	*Indeterminate result*	*Total*
Rosaramicin 1 g daily for 7 days	40	4	2	0	46
Tetracycline 1 g daily for 7 days	37	6	2	3	48

with tetracycline (in nine as the sole pathogen and in seven in association with *U urealyticum*). Chlamydia were not reisolated from any of these patients during the follow-up period (table II). Differences in responses between those given rosaramicin and those given tetracycline were not significant.

TABLE II *Effect of treatment of non-gonococcal urethritis with rosaramicin or tetracycline on associated Chlamydia trachomatis and Ureaplasma urealyticum. (Figures in parentheses show numbers with complete clinical resolution)*

Isolation sequence	*No of patients treated with:*	
	Rosaramicin	*Tetracycline*
Chlamydia trachomatis		
Positive – positive	1 (0)	0
Positive – negative	17 (17)	16 (15)
Negative – positive	0	0
Negative – negative	28 (23)	32 (22)
Ureaplasma urealyticum		
Positive – positive	2 (1)	4 (3)
Positive – negative	12 (11)	15 (12)
Negative – positive	6 (5)	2 (2)
Negative – negative	26 (23)	27 (20)

Ureaplasma urealyticum

U urealyticum was isolated from 14 of 46 (30%) patients before treatment with rosaramicin and was reisolated from two of these patients during follow up; one showed signs of persistent urethritis but the other was clinically cured. In a further six patients *U urealyticum* was recovered during follow up although they had been isolation-negative before treatment; one showed persistent urethritis but the other five were clinically cured. *U urealyticum* was isolated from 19 of 48 (39%) men before treatment with tetracycline. It was reisolated from four of these patients during follow up; one showed persistent urethritis but three were clinically cured. In a further two patients *U urealyticum* was recovered during follow up although they had been isolation-negative before treatment; both were clinically cured (table II). Differences in responses between those given rosaramicin and those given tetracycline were not significant.

SIDE EFFECTS

No evidence of haematological or biochemical toxicity was noted in any patients treated with rosaramicin or tetracycline. In one man who was treated with rosaramicin liver function tests before treatment gave abnormal results. Total bilirubin was 39 μmol/l, conjugated bilirubin 4 μmol/l, alanine transaminase 94 IU/l, and y-glutamyl transferase 172 IU/l. Serum HBsAg was not present. A slight increase in these enzyme concentrations was noted after therapy; over the following six months they returned to within normal limits, although there was a persistent unconjugated bilirubinaemia. He probably had pre-existing Gilbert's disease with a mild attack of viral hepatitis unrelated to rosaramicin therapy.

Minor gastrointestinal side effects (nausea, diarrhoea, and abdominal discomfort) were described by 15 of the 46 (33%) men treated with rosaramicin; headache, dizziness, or fatigue were noted by three others. Gastrointestinal side effects were described by two of the 48 (4%) men treated with tetracycline; headaches or dizziness were noted by four others. The differences in gastrointestinal side effects between men treated with rosaramicin and tetracycline were significant ($P = 0{\cdot}01$).

Discussion

Thus, rosaramicin and tetracycline give similar results in the treatment of NGU, with no significant differences in the responses of *C trachomatis* or *U urealyticum* to either drug. Clinical recovery correlated well with the elimination of *C trachomatis* but less well with that of *U urealyticum*. There was a relatively high incidence of gastrointestinal side effects in men treated with rosaramicin which may limit its clinical use.

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